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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,411	11/10/2005	Clifford Charles Shone	1581.0130005/TJS/JJY	7312

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STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
01/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,411	SHONE ET AL	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/6/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *31-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed 10-6-08. Claims 1 and 18 have been amended. Claims 1-41 are pending. Claims 31-41 are withdrawn. Claims 1-30 are under examination. Amendments to claims have been entered.

Claim Rejections Maintained - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. The rejection of claims 1-30 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter are maintained for the reason set forth in the previous office action.

Applicant arguments:

The Examiner rejected claims 1-30 under 35 U.S.C. § 101 because the claims are allegedly directed to non-statutory subject matter. The Examiner contends that the claims are directed to products of nature, and as such, are not patentable, because they do not reflect the "hand of man." The Examiner suggests recitation of "isolated polypeptide," for example. Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner. Applicants respectfully point out that in contrast to clostridial neurotoxin holotoxin, the presently claimed single- chain polypeptides are incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds. In addition, the presently claimed single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc. Furthermore, the specific SEQ ID NOs recited in claim 1 include one or more features that are not present in "native" clostridial

neurotoxins, such as, at least one of a non-native protease activation site, spacer/linker peptide, C-terminal peptide ligand/tag, N-terminal extension and/or amino acid variation(s).

Hence, the claimed invention reflects "the hand of man" and is not directed towards non-statutory subject matter. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Examiner's Response to Applicant's Arguments:

Applicant's Arguments are considered but not deemed persuasive. The claims are drawn to a single chain polypeptide comprising a SEQ ID NO. The claims are further drawn to first and second domains in a polypeptide which occurs naturally in a polypeptide structure. Thus the polypeptide does not indicate the hand of man because the polypeptide can naturally occur and are deemed products of nature.

As outlined previously, the claimed invention is drawn to a product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process.

The claimed invention is drawn to a product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Additionally, purity of naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. Merck co. V. Chase Chemical Co. 273 F. Supp 68 (1967). See also American Wood v. Fiber Disintegrating Co., 90 US 566 (1974);American Fruit Growers v. Brogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. V. Kalo Innoculant Co. 33 US 127 (1948). In the instant case recitation of a polypeptide does not indicate the hand of man because the polypeptide can naturally occur and are deemed products of nature. Applicant(s) can recite, for example, 'isolated polypeptide' provided there is support in the disclosure to reflect the hand of man for the products used in the methods.

Claim Rejections Maintained - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. The rejections of claim 1-30 under 35 U.S.C. 102(b) as being anticipated by Binz et al 1990 Eur. J. Biochem. 189:73-8 is maintained for the reasons set forth in the previous office action.

Applicant arguments:

Binz et al. teach a fragment of SEQ ID NO:66 which anticipate the claims. The Examiner alleges that the Binz et al. polypeptide fragment is capable of cleaving vesicle/plasma membrane associated proteins essential to exocytosis. Applicants respectfully traverse this rejection.

Applicants respectfully assert that the claims are novel over Binz et al. The sequence recited in Binz et al. is full length BoNT/A holotoxin, and therefore comprises a functional C-terminal part of a clostridial neurotoxin heavy chain designated Ho In contrast, the pending claims explicitly recite the absence of a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc. Accordingly, the single-chain polypeptide of the present invention lacks the ability to bind to cell surface receptors that are the natural cell surface receptors to which the native clostridial neurotoxin binds. Accordingly, Applicants respectfully submit that the pending claims are novel over Binz et al., and Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Examiner's Response:

Examiner has accepted Applicant's amendments. Applicant's arguments have been considered but have not been found persuasive.

The claims are drawn to a single chain polypeptide comprising first and second domains, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; and wherein: said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; wherein said single chain polypeptide comprises a sequence selected from the group consisting of
(I)
SEQ ID NO: 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 139, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161,163, 165, 167, 169, 171,173, and 175; or
(II) a fragment or variant of (I) having a first domain that is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis.

As to Applicant's Assertion above, Examiner interprets the single chain polypeptide as claimed as set forth supra comprising first and second domains, further comprising SEQ ID NO 66; or a single chain polypeptide as claimed as set forth supra comprising first and second domains, further comprising a fragment or variant thereof. Thus although the sequence recited in Binz et al. is a full length BoNT/A holotoxin. The limitations of the claim allow for the full length molecule, because the claim is drawn to a fragment or variant thereof, i.e., the full length molecule is a "variant" of the claimed molecule which lacks a functional C-terminal. Therefore limitations have been met.

As outlined previously, the claims The claims are drawn to a single chain polypeptide comprising first and second domains, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; and wherein: said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; wherein said single chain polypeptide comprises a sequence selected from the group consisting of (I) SEQ ID NO: 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 139, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161,163, 165, 167, 169, 171,173, and 175; or (II) a fragment or variant of (I) having a first domain that is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis.

Binz et al teach a fragment of SEQ ID NO: 66 (see STIC RESULTS). The fragment of SEQ ID NO: 66 of Binz et al is inherently capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis, wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain, wherein said clostridial toxin heavy chain is a tetanus neurotoxin heavy chain, wherein the first domain exhibits endopeptidase activity specific for a substrate of SNAP-25, synaptobrevin/VAMP and syntaxin, wherein said second domain is a clostridial toxin heavy chain HN portion, wherein said clostridial neurotoxin heavy chain is a botulinum

neurotoxin type A chain, wherein the second domain comprises the 423 N-terminal amino acids of botulinum toxin type A heavy chain, wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain, wherein the second domain comprises the 107 N-terminal amino acids of a botulinum toxin type B heavy chain, wherein the second domain comprises the 417 N-terminal amino acids of botulinum toxin type B heavy chain, wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain, wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain, further comprising a site for cleavage by a proteolytic enzyme, wherein the cleavage site is not present in a native clostridial neurotoxin, wherein the cleavage site allows proteolytic cleavage of the first and second domains, wherein the cleavage site allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein than does the-polypeptide prior to said proteolytic cleavage, wherein the fragment is obtainable by providing a first nucleic acid sequence encoding said cleavage site within a second nucleic acid sequence encoding said single chain polypeptide a peptide, wherein the second domain lacks a C-terminal part of a clostridial neurotoxin heavy chain designated Hc, further comprising a third domain that binds the polypeptide to a cell, by binding of the third domain directly to a cell or by binding of the third domain to a ligand or to ligands that bind to a cell, wherein said third domain is for binding the polypeptide to an immunoglobulin, wherein said third domain is a tandem repeat synthetic IgG binding domain derived from domain b of Staphylococcal protein A, wherein said third domain comprises an amino acid sequence that binds to a cell surface receptor, wherein said third domain is insulin-like growth factor-1 (IGF-1), further comprising a spacer molecule between the first and second domains, further comprising a spacer molecule between the second and third domains, further comprising a purification tag that binds to an affinity matrix thereby facilitating purification of the polypeptide using said matrix, further comprising a spacer molecule between the purification tag and the polypeptide, wherein said purification tag binds to an affinity matrix of glutathione sepharose, wherein a first protease cleavage site is

incorporated between said single chain polypeptide the polypeptide and the purification tag, said protease cleavage site enabling proteolytic separation of said polypeptide from said purification tag, wherein a second proteolytic cleavage site is incorporated between the first and second domains of said single chain polypeptide the polypeptide.

Status of the Claims

4. No claims are allowed.

Claim 1-30 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie
Examiner
GAU 1645
REM 3B31

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645